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Review Article

A review on self-emulsified drug delivery system

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ABSTRACT

Improving oral bioavailability of low poorly water soluble drugs using self-emulsifying drug delivery systems (SEDDS) possess significant potential. Oral bioavailability of hydrophobic drugs can be improved using SEDDS, and appears most promising. Their dispersion in gastro intestinal (GI) fluid after administration forms micro or nano emulsified drug which gets easily absorbed through lymphatic pathways bypassing the hepatic first pass metabolism. Parameters like surfactant concentration, oil to surfactant ratio, polarity of emulsion, droplet size and charge on droplet plays a critical role in oral absorption of drug from SEDDS. For hydrophobic drug substances that exhibit dissolution step as rate limiting for absorption, SEDDS offer an improvement in rate and extent of absorption and gives more reproducible plasma concentration time profiles. Use of combined *in vitro* dispersion and digestion methodologies has enabled a much improved understanding of role of intestinal lipid processing on solubilization behavior of lipid based drug delivery systems (LBDDS). The article gives a brief view on the solid lipid nanoparticles and its evaluation.

Keywords: Self-Emulsifying formulation, Lipid-based drug delivery systems, Characterization, Bioavailability enhancement

Introduction

Self emulsifying drug delivery system (SEDDS) is defined as isotropic mixture of oil and surfactants or alternatively one or more hydrophilic solvents and co-solvents. Upon mild agitation followed by dilution in aqueous media such as the gastrointestinal (GI) fluid, these systems can form fine oil in water (o/w) emulsions or micro emulsions. Self micro emulsifying formulations spread readily in the GI tract and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification (SEDDS) typically produce emulsion with a droplet size between 100 and 300 nm while SMEDDS form transparent micro emulsion with a droplet size of less than 50 nm. When compared with emulsions which are sensitive and metastable dispersed forms, SEDDS and SMEDDS are physically stable formulations that are easy to manufacture. SMEDDS can be formulated to give sustained release dosage form by adding polymeric matrix, which is not ionizable at physiological pH and after ingestion in contact with GI fluid forms a gelled polymer making it possible to release the micro emulsified active

agent in a continuous and sustained matter by diffusion. Bases of self micro emulsifying system have been formulated using medium chain triglyceride oils and non-ionic surfactant which are acceptable for oral ingestion. The lipophilic (poorly water soluble) drugs such as nifedipine, griseofulvin, cyclosporine, digoxin, itrconazole, carbamazepine, piroxicam, steroids, ibuprofen, diazepam, etc. are formulated in SMEDDS to improve efficacy and safety. It should be noted that water-in-oil version of SMEDDS has also been investigated. This system can be liquid but also semisolid depending on the excipient's choice. These are traditionally designed for the oral route. These preparations can be given as soft or hard gelatin capsules for easy administration and precise dosage.

The better absorbed drugs across the gastrointestinal tract (GIT) provide good oral bioavailability but have number of potentially limiting factors. These include appropriate stability and solubility in the GI fluid, reasonable intestinal permeability, and resistance to metabolism both within the enterocyte and the liver.[1] It has realized that the oral bioavailability of poorly water soluble, lipophilic drugs may be enhanced when coadministered with a meal rich in fat this has led to increase recent interest in the formulation of poorly soluble drugs in lipids as a means to enhance drug solubilisation in the GIT.[2-7] Lipid-based formulations not only improve but normalize drug absorption, which is particularly beneficial for low therapeutic index drugs.[8-10] These formulations can also enhance drug absorption by a number of ancillary mechanisms, e.g. (a) including inhibition of P-glycoprotein-mediated drug efflux and pre absorptive metabolism by gut membrane-bound cytochrome enzymes (b) promotion of lymphatic transport, which delivers drug directly to the systemic circulation while avoiding hepatic first-pass metabolism and (c) by increasing GI membrane permeability.[11-15] Modification of the physicochemical properties, such as salt formation and particle size reduction of the compound may be one approach to improve the dissolution rate of the drugs.[16,17] However, these methods have their own limitations. In recent years much attention has focused on lipid−based formulations to improve the oral bioavailability of poorly soluble drugs .In fact, the most popular approach is the incorporation of the drug compound into inert lipid vehicles such as oils, surfactant dispersions, self-emulsifying formulations, emulsions and liposomes with particular emphasis on self-emulsifying drug delivery systems (SEDDS).

Novelty statement

This review on Self Emulsifying Drug Delivery Systems (SEDDS) is written as these drug delivery systems have unparalleled prospect in enhancing bioavailability of low soluble drugs of biopharmaceutical classification. An extensive and updated description of literature reports on different types of self emulsifying formulations, techniques employed, characterization, optimization and application strategies are discussed comprehensively to direct the formulation scientists in formulating a stable, safe and effective self emulsifying formulation. The figures are self designed to prove the concept, mechanism and meaning of SEDDS.

Self-emulsifying drug delivery systems (SEDDS)

SEDDS belong to lipid-based formulations. Lipid formulations can be oils, surfactant dispersions, emulsions, solid lipid nanoparticles and liposomes. SEDDS are isotropic mixtures of drug, lipids and surfactants, usually with one or more hydrophilic co-solvents or co-emulsifiers. Upon mild agitation followed by dilution with aqueous media, these systems can form fine (oil in water) emulsion instantaneously. 'SEDDS' is a broad term, typically producing emulsions with a droplet size ranging from a few nanometers to several-microns. "Self micro-emulsifying drug delivery systems" (SMEDDS) indicates the formulations forming transparent microemulsions with oil droplets ranging between 100 and 250 nm. "Self-nano-emulsifying drug delivery systems" (SNEDDS) is a recent term with the globule size ranges less than 100 nm.[18] A schematic about self-micro-emulsifying drug delivery systems" (SMEDDS) is shown in Figure 1.

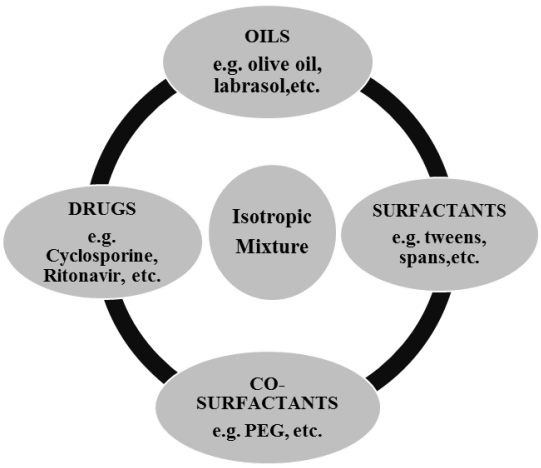

Figure 1: Illustration of what is SEDDS.

It has been suggested that self-emulsifying drug delivery systems can be prepared which, after oral administration in gelatin capsules, will emulsify within the gastric contents.[19] Advantage of self-emulsifying formulations over solid dosage formulations is the avoidance of slow drug dissolution. Distribution of the emulsion within the GIT helps to avoid the irritancy. Some marketed self emulsified dosage forms are described in Table 1.

Table 1: Marketed self emulsified dosage forms.

Drug name	Compound	Dosage form	Company
Neoral	Cyclosporin	Soft gelatin capsules	Novartis
Norvir	Ritonavir	Soft gelatin capsules	Abott laboratories
Fortavase	Saquinavir	Soft gelatin capsules	Hoffmann-LaRoche Inc.
Agenerase	Amprenavir	Soft gelatin capsules	Glaxosmithkline
Solufen	Ibuprofen	Hard gelatin capsules	Sanofi-Aventis
Solufen	Fenofibrate	Hard gelatin capsules	Sanofi-Aventis

Need of SEDDS

Oral delivery of poorly water-soluble compounds is to pre-dissolve the compound in a suitable solvent and fill the formulation into capsules. The main benefit of this approach is that predissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, a potential problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract, particularly if a hydrophilic solvent is used (e.g. polyethylene glycol). If the drug can be dissolved in a lipid vehicle there is less potential for precipitation on dilution in the GI tract, as partitioning kinetics will favor the drug remaining in the lipid droplets. Another strategy for poorly soluble drugs is to formulate in a solid solution using a water-soluble polymer to aid solubility of the drug compound. For example, polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG 6000) have been used for preparing solid solutions with poorly soluble drugs. One potential problem with this type of formulation is that the drug may favor a more thermodynamically stable state, which can result in the compound crystallizing in the polymer matrix. Therefore the physical stability of such formulations needs to be assessed using techniques such as differential scanning calorimetry or X-ray crystallography. In this type of case SEDD system is a good option.[20-22]

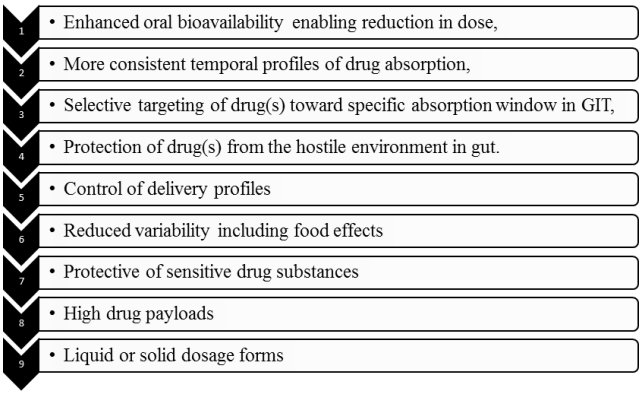

Figure 2: Potential advantages of these systems.

Limitations of SEDDS

- Chemical instabilities of drug and high surfactant concentrations
- The large amount of surfactant in self-emulsifying formulations (30-60%) irritates GIT
- Moreover, volatile co-solvent in the conventional self-emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsule, resulting in the precipitation of the lipophilic drug.[23]

Mechanism of SEDDS

Different approaches have been reported in the literature. No single theory explains all aspects of micro emulsion formation. Schulman et al. considered that the spontaneous formation of micro emulsion droplets was due to the formation of a complex film at the oil-water interface by the surfactant and co-surfactant. Thermodynamic theory of formation of micro emulsion explains that emulsification occurs, when the entropy change that favour dispersion is greater than the energy required to increase the surface area of the dispersion and the free energy (ΔG) is negative. The free energy in the micro emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by the equation:

$$\Delta G = \Sigma N_{Л} r2 \sigma$$

Where, ΔG is the free energy associated with the process (ignoring the free energy of the mixing). N is the number of droplets of radius r and σ are presents the interfacial energy. With time, the two phases of the emulsion tend to separate to reduce the interfacial area, and subsequently, the free energy of the system decreases. Therefore, the emulsion resulting from aqueous dilution are stabilized by conventional emulsifying agents, which forms a mono layer around the emulsion droplets, and hence, reduce the interfacial energy, as well as providing a barrier to prevent coalescence.[24]

Lipid formulation classification system (LFCS)

LFCS was established by Pouton in 2000 and recently updated (2006) to help stratify formulations into those with similar component parts.[25] The LFCS briefly classifies lipid-based formulations into four types according to their composition and the possible effect of dilution and digestion on their ability to prevent drug precipitation. A schematic illustration on lipid formulation classification system is given in Table 2.

Type I lipid formulations

It consist of formulations which comprise drug in solution in triglycerides and/or mixed glycerides or in an oil in water emulsion stabilized by low concentrations of emulsifiers such as 1% (w/v) polysorbate 60 and 1.2% (w/v) lecithin.[26] Generally, these systems exhibit poor initial aqueous dispersion and require digestion by pancreatic lipase/ co-lipase in the GIT to generate more amphiphilic lipid digestion products and promote drug transfer into the colloidal aqueous phase. Type I lipid formulations therefore represent a relatively simple formulation option for potent drugs or highly lipophilic compounds where drug solubility in oil is sufficient to allow incorporation of the required payload (dose).[27]

Type II lipid formulations

Self-emulsification is generally obtained at surfactant contents above 25% (w/w). However, at higher surfactant contents (greater than 50–60% (w/w) depending on the materials) the progress of emulsification may be compromised by the formation of viscous liquid crystalline gels at the oil/water interface.[28,29] Type II lipid-based formulations provide the advantage of overcoming the slow dissolution step typically observed with solid dosage forms and as described above generate large interfacial areas which in turn allows efficient partitioning of drug between the oil droplets and the aqueous phase from where absorption occurs.[30,31]

Table 2: Lipid formulation classification system (LFCS) as described by Pouton showing typical compositions and properties of lipid based formulations.

Composition	Type I OIL	Type II SEDDS	Type III A SEDDS	Type III B SMEDDS	Type IV OIL- Free
Glycerides(TG,DG, MG)	100%	40-80%	40-80%	< 20%	-
Water insoluble Surfactants(HLB <12)	-	20-60%	-	-	0-20%
Water soluble surfactants(HLB > 12)	-	20-40%	-	20-50%	20-80%
Hydrophilic co-solvents	-	-	0-40%	20-50%	0-80%
Particle size of dispersion(nm)	Coarse	100-250	100-250	50-100	< 50
Significance of aqueous Dilution	Ltd. importance	Solvent capacity unaffected	Some loss of solvent capacity	Significant phase changes and potential loss of solvent capacity	Significant phase changes and potential loss of solvent capacity
Significance of digestibility	Crucial need	Not crucial but likely to occur	Not crucial but may be inhibited	Not required	Not required

Type III lipid formulation

Commonly referred to as self-microemulsifying drug delivery systems (SMEDDS), are defined by the inclusion of hydrophilic surfactants (HLB>12) and co-solvents such as ethanol, propylene glycol and polyethylene glycol. Type III formulations can be further segregated (somewhat arbitrarily) into Type IIIA and Type IIIB formulations in order to identify more hydrophilic systems (Type IIIB) where the content of hydrophilic surfactants and co-solvents increases and the lipid content reduces. Type IIIB formulations typically achieve greater dispersion rates when compared with Type IIIA although the risk of drug precipitation on dispersion of the formulation is higher given the lower lipid content.

Type IV lipid formulation

In order to capture the recent trend towards formulations which contain predominantly hydrophilic surfactants and cosolvents, this category was recently added.[25]Type IV formulations do not contain natural lipids and represent the most hydrophilic formulations. These formulations commonly offer increased drug payloads when compared to formulations containing simple glyceride lipids and also produce very fine dispersions when introduced in aqueous media. Little is known however, as to the solubilisation capacity of these systems in

vivo and in particular whether they are equally capable of maintaining poorly water soluble drug in solution during passage along the GIT when compared with formulations comprising natural oils (Type II and Type III). An example of a Type IV formulation is the current capsule formulation of the HIV protease inhibitor amprenavir (Agenerase) which contains TPGS as a surfactant and PEG 400 and propylene glycol as co-solvents.[32]

Excipients used in SMEDDS

Pharmaceutical acceptability of excipients and the toxicity issues of the components used makes the selection of excipients really critical. There is a great restriction as which excipients to be used. Early studies revealed that the self-microemulsification process is specific to the nature of the oil/surfactant pair, the surfactant concentration and oil/surfactant ratio, the concentration and nature of co-surfactant and surfactant/co-surfactant ratio and the temperature at which self-microemulsification occurs. These important discoveries were further supported by the fact that only very specific combinations of pharmaceutical excipients led to efficient self- microemulsifying systems.

Oils

The oil represents one of the most important excipients in the SMEDDS formulation not only because it can solubilize the required dose of the lipophilic drug or facilitate self emulsification but also and mainly because it can increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglyceride.[33] Both long and medium chain triglyceride (LCT and MCT) oils with different degrees of saturation have been used for the design of self-emulsifying formulations. Furthermore, edible oils which could represent the logical and preferred lipid excipients choice for the development of SMEDDS are not frequently selected due to their poor ability to dissolve large amounts of lipophilic drugs. Modified or hydrolyzed vegetable oils have been widely used since these excipients form good emulsification systems with a large number of surfactants approved for oral administration and exhibit better drug solubility properties.[34] They offer formulative and physiological advantages and their degradation products resemble the natural end products of intestinal digestion. Novel semisynthetic medium chain derivatives, which can be defined as amphiphilic compounds with surfactant properties, are progressively and effectively replacing the regular medium chain triglyceride oils in the SMEDDS.[35] This is in accordance with findings of Deckelbaum (1990) showing that MCT is more soluble and have a higher mobility in the lipid/water interfaces than LCT associated with a more rapid hydrolysis of MCT. In general, when using LCT, a higher concentration of cremophor RH40 was required to form microemulsions compared with MCT.

E.g.: Cotton seed oil, Soybean oil, Corn oil, Sunflower oil, Castor oil etc.

Surfactants

Several compounds exhibiting surfactant properties may be employed for the design of self-emulsifying systems, but the choice is limited as very few surfactants are orally acceptable. The most widely recommended ones being the non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB). The commonly used emulsifiers are various solid or liquid ethoxylated polyglycolyzed glycerides and polyoxyethylene oleate. Safety is a major determining factor in choosing a surfactant. Emulsifiers of natural origin are preferred since they are considered to be safer than the synthetic surfactants.[36] However, these surfactants have a limited self-emulsification capacity. Non-ionic surfactants are less toxic than ionic surfactants but they may lead to reversible changes in the permeability of the intestinal lumen.[37] The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of SMEDDS.

There is a relationship between the droplet size and the concentration of the surfactant being used. In some cases, increasing the surfactant concentration could lead to droplets with smaller mean droplet size, this could be explained by the

stabilization of the oil droplets as a result of the localization of the surfactant molecules at the oil-water interface.[38] On the other hand, in some cases the mean droplet size may increase with increasing surfactant concentrations.[39] This phenomenon could be attributed to the interfacial disruption elicited by enhanced water penetration into the oil droplets mediated by the increased surfactant concentration and leading to ejection of oil droplets into the aqueous phase.[40] The surfactants used in these formulations are known to improve the bioavailability by various mechanisms including: improved drug dissolution, increased intestinal epithelial permeability, increased tight junction permeability and decreased/inhibited pglycoprotein drug efflux. However, the large quantity of surfactant may cause moderate reversible changes in intestinal wall permeability or may irritate the GI tract. Formulation effect and surfactant concentration on gastrointestinal mucosa should ideally be investigated in each case.

Surfactant molecules may be classified based on the nature of the hydrophilic group within the molecule. The four main groups of surfactants are defined as follows,

1. Anionic surfactants
2. Cationic surfactants
3. Ampholytic surfactants
4. Nonionic surfactants

Anionic Surfactants: where the hydrophilic group carries a negative charge such as carboxyl (RCOO-), sulphonate (RSO3-) or sulphate (ROSO3-). Examples: Potassium laurate, sodium lauryl sulphate.

Cationic surfactants: where the hydrophilic group carries a positive charge. Example: quaternary ammonium halide.

Ampholytic surfactants: (also called zwitter ionic surfactants) contain both a negative and a positive charge. Example: sulfobetaines.

Nonionic surfactants: where the hydrophilic group carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene (OCH_2CH_2O). Examples: Sorbitan esters (Spans), polysorbates (Tweens).

Co-solvents

The production of an optimum SEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants, thus the concentration of surfactant can be reduced by incorporation of co surfactant. Role of the co-surfactant together with the surfactant is to lower the interfacial tension to a very small even transient negative value. At this value the interface would expand to form fine dispersed droplets, and subsequently adsorb more surfactant and surfactant/co-surfactant until their bulk condition is depleted enough to make interfacial tension positive again. This process known as 'spontaneous emulsification' forms the microemulsion. However, the use of co-surfactant in self emulsifying systems is not mandatory for many non-ionic surfactants. The selection of surfactant and co-surfactant is crucial not only to the formation of SEDDS, but also to solubilization of the drug in the SEDDS. Organic solvents, suitable for oral administration (ethanol, propylene glycol (PG), polyethylene glycol (PEG), etc.) may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base and can act as co-surfactant in the self emulsifying drug delivery systems, although alcohol- free self-emulsifying microemulsions have also been described in the literature. Indeed, such systems may exhibit some advantages over the previous formulations when incorporated in capsule dosage forms, since alcohol and other volatile co-solvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft gelatin or hard sealed gelatin capsules resulting in the precipitation of the lipophilic drug. On the other hand, the lipophilic drug dissolution ability of the alcohol free formulation may be limited. Hence, proper choice has to be made during selection of components.[41]

Co-surfactant

In SMEDDS, generally co-surfactant of HLB value 10-14 is used. Hydrophilic co-surfactants

are preferably alcohols of intermediate chain length such as hexanol, pentanol and octanol which are known to reduce the oil water interface and allow the spontaneous formulation of micro emulsion. E.g. span, capyrol 90, capmul.[42,43]

Recent dosage form development in SEDDS

1. Dry emulsions
2. Self- emulsifying capsules
3. Self- emulsifying sustained/controlled-release tablets
4. Self- emulsifying sustained/controlled-release pellets
5. Self emulsifying solid dispersions
6. Self emulsifying beads
7. Self emulsifying Sustained release microspheres
8. Self-emulsifying nanoparticles
9. Self-emulsifying suppositories
10. Self emulsifying implants.[44-51]

Drug properties suitable for SEDDS

1. Dose should not be so high
2. Drug should be oil soluble
3. High melting point drug is poorly suited to sedds
4. Log P Value should be high.

Characterization of SEDDS

The very essence of SEDDS is self-emulsification, which is primarily assessed visually. The various ways to characterize SEDDS are compiled below.

1. *Equilibrium phase diagram:* Although self emulsification is a dynamic non equilibrium process involving interfacial phenomena, information can be obtained about self-emulsification using equilibrium phase behavior.
2. *Turbidity measurement:* This identifies efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time. These measurements are carried out on turbidity meters, most commonly the Hach turbidity meter and the Orbeco-Helle turbidity meter.
3. *Droplet size:* This is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release, as well as the stability of the emulsion. Photon correlation spectroscopy, microscopic techniques or a Coulter Nano-sizer are mainly used for the determination of the emulsion droplet size. Electron microscopic studies: Freeze-fracture electron microscopy has been used to study surface characteristics of dispersed systems.
4. *Zeta potential measurement:* This is used to identify the charge of the droplets. In conventional SEDDS, the charge on an oil droplet is negative because of the presence of free fatty acids.
5. *Determination of emulsification time:* The process of self-emulsification was observed using light microscopy. The mechanism of emulsification involved erosion of a fine cloud of small particles from the surface of large droplets, rather than a progressive reduction in droplet size.
6. *Liquefaction time:* This test is designed to estimate the time required by solid SEDDS to melt *in vivo* in the absence of agitation to simulated GI conditions.
7. *Small-angle neutron scattering:* Small-angle neutron scattering can be used to obtain information on the size and shape of the droplets.
8. *Small-angle X-ray scattering:* Small-angle X-ray scattering is capable of delivering structural information of macromolecules between 5 and 25 nm, of repeat distances in partially ordered systems of up to 150 nm. It is used for the determination of the microscale or nanoscale structure of particle systems in terms of such parameters as averaged particle sizes, shapes, distribution and surface-to-volume ratio.[52-59]

Solid self-emulsifying drug delivery system (S-SEDDS)

S-SEDDS mean solid dosage forms with self-emulsification properties. S-SEDDS focus on

the incorporation of liquid/semisolid SE ingredients into powders/nanoparticles by different solidification techniques (e.g. adsorptions to solid carriers, spray drying, melt extrusion, nano-particle technology).

In the 1990s, S-SEDDS were usually in the form of SE capsules, SE solid dispersions and dry

Emulsions, but other solid SE dosage forms have emerged in recent years, such as SE pellets/tablets, SE microspheres/nanoparticles and SE suppositories/implants. SEDDS are usually, however, limited to liquid dosage forms, because many excipients used in SEDDS are not solids at room temperature.

Solidification techniques for transforming liquid / semisolid SEDDS to solid SEDDS

Capsule filling with liquid and semisolid self-emulsifying formulations

Capsule filling is the simplest and the most common technology for the encapsulation of liquid or semisolid SE formulations for the oral route. In parallel with the advances in capsule technology proceeding, liquid-Oros technology (Alza Corporation) has been designed for controlled delivery of insoluble drug substances or peptides. This system is based on osmotic principles and is a liquid SE formulation system. It consists of an osmotic layer, which expands after coming into contact with water and pumps the drug formulation through an orifice in the hard or soft capsule. A primary consideration in capsule filling is the compatibility of the excipients with the capsule shell. The liquid/semisolid lipophilic vehicles compatible with hard capsules were listed by.[60] The advantages of capsule filling are simplicity of manufacturing, suitability for low dose highly potent drugs and high drug loading (up to 50% (w/w) potential.

Spray drying

This technique involves the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers, and solubilization of the mixture before spray drying. The solubilized liquid formulation is then atomized into a spray of droplets. The droplets are introduced into a drying chamber, where the volatile phase (e.g. the water contained in an emulsion) evaporates, forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared into tablets or capsules.

Spray cooling

Spray cooling also referred to as spray congealing is a process whereby the molten formula is sprayed into a cooling chamber. Upon contact with the cooling air, the molten droplets congeal and re-crystallize into spherical solid particles that fall to the bottom of the chamber and subsequently collected as fine powder. The fine powder may then be used for development of solid dosage forms, tablets or direct filling into hard shell capsules. Many types of equipment are available to atomize the liquid mixture and to generate droplets: rotary pressure, two-fluid or ultrasonic atomizers.[60, 61]

Adsorption to solid carriers

SEDDS can be adsorbed at high levels (up to 70% (w/w)) onto suitable carriers. Solid carriers can be microporous inorganic substances, high surface area colloidal inorganic adsorbent substances, cross-linked polymers or nanoparticle adsorbents (e.g., silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum, crospovidone, cross-linked sodium carboxymethyl cellulose and cross-linked polymethyl methacrylate). The adsorption technique has been successfully applied to gentamicin and erythropoietin with caprylocaproyl polyoxylglycerides (Labrasol) formulations that maintained their bioavailability enhancing effect after adsorption on carriers.[62-64]

Melt granulation

Melt granulation or pelletization is a one step-process allowing the transformation of a powder mix (containing the drug) into granules or spheronized pellets. The technique needs high shear mixing in presence of a meltable binder.

This is referred to as "pump-on" technique. Alternatively, the binder may be blended with the powder mix in its solid or semi-solid state and allowed to melt (partially or completely) by the heat generated from the friction of particles during high shear mixing referred to as "melt-in" process. The melted binder forms liquid bridges with the powder particles that shape into small agglomerates (granules) which can, by further mixing under controlled conditions transform to spheronized pellets.[65-67]

Melt extrusion/extrusion spheronization

It is a solvent-free process that allows high drug loading (60%) as well as content uniformity. Applying extrusion-spheronization, SE pellets of diazepam and progesterone and bi-layered cohesive SE pellets have been prepared.[68,69]

Bioavailability enhancement

Oral drug bioavailability of a chemically stable drug is limited by its solubility and its permeability. Poor drug absorption therefore can be caused by inadequate rate and extent of drug dissolution and or low permeation. Accordingly as per the biopharmaceutical classification system, a drug on the basis of these solubility

Table 3: Literature updates on various reports of bioavailability enhancement using self-emulsifying formulations.

Drug	Enhancement	With reference to	Species
Acyclovir	3.5 fold	Pure drug solution	Male albino rats
Anethole trithione	2.5 fold	Tablets	Rabbits
Atorvastatin	1.5 fold	Conventional tablet	Beagle dogs
Bicalutamide	2 fold	Suspension	Rats
Carvedilol	4.13 fold	Commercial tablet	Beagle dogs
Carvedilol	1.56 fold	Luode (a commercial tablet)	Beagle dogs
Danazold	2 fold	Pure surfactant solution	Beagle dogs
Fenofibrate	1.075 fold	Tricor tablets	Human
Gentamycin	5 fold	I.V saline	Beagle dogs
Insulin	1.15 fold	Subcutaneous injection	Beagle dogs
Itraconazole	1.9-2.5 fold	Sporanox capsules	Humans
Itraconazole	2 fold	Solid dispersion	Rats
Ketoconazole	2 fold	Pure drug	Rats
Ketoprofen	1.13 fold	Pure drug	Humans
Mitotane	3.4 fold	Lysodren	Rabbits
Nimodipine	2.6-6.6 fold	Conventional tablet	New Zealand Male rabbits
Nimodipine	4.6 fold 1.91 fold 1.53 fold	Suspension Oily solution Micellar solution	Male rabbits
Nitrendipine	1.6 fold	Conventional tablet	Beagle dogs
Silymarin	3.6 fold	Legalon capsule	Rats
Oleanolic acid	2.4 fold	Tablet	Rats
Simvastatin	1.5 fold	Zocor tablets	Beagle dogs
Tretinoin	1.67 fold	Commercial capsule formulation	Beagle dogs

and permeability characteristics classified in to four possible categories, class I to IV.

Bioavailability of poorly soluble class II drugs, on the contrary is dependent on their aqueous solubility/ dissolution rate. As these drugs tend to exhibit dissolution limited bioavailability, the in vivo physiological response is well correlated with the in vitro dissolution, resulting eventually in good in vitro/in vivo correlations (IVIVC).

For accomplishing better solubility or dissolution rate of class II drugs use of techniques like micronization, co solvents, micellar solubilization, solid dispersions and complexation has been employed with fruition.[70] a report on bioavailability enhancement using self emulsifying formulation by different workers is presented in Table 3.[71-76]

Conclusions

Self-emulsifying drug delivery systems are a promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SEDDSs, which have been shown to substantially improve oral bioavailability. With future development of this technology, SEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

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